REVIEW ARTICLE

Treatment of hay fever

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SUMMARY. The range of treatments for hay fever available to the general practitioner has changed considerably in recent years. New antihistamines have addressed the problem of sedation and moved towards one daily dose; nasally applied corticosteroids avoid the need for systemic steroid therapy and its potential adverse effect; and regulatory decisions have set a trend away from immunotherapy in general practice. However, knowledge about the mechanism of action of immunotherapy is increasing and new developments with improved safety profiles include allergen polymers, allergoids, oral immunotherapy and nasal immunotherapy. Choice of treatment depends, as always, on the individual circumstances of the patient and his or her disease.

Introduction

THERE have been several developments in the treatment of hay fever in recent years. The introduction of the new generation of non-sedative antihistamines and a partly-enforced discontinuation of immunotherapy in general practice in the United Kingdom have affected choice of treatment by doctors and their patients. In an effort to tackle the question of the safety of immunotherapy and to explain its mode of action, considerable work has been published, much of it from the United States of America and Scandinavia. Various modifications of conventional immunotherapy have been examined and oral and nasal immunotherapy have been submitted to clinical trial. This article reviews these developments and considers drugs, as yet unavailable for routine clinical use in hay fever, such as nedocromil sodium and levocabastine.

Sensible advice to hay fever sufferers remains a good starting point and avoidance measures may at least lessen the severity of symptoms for some patients. With the availability of an increasing range of satisfactory treatments for hay fever, certain measures now have less of a part to play; these include nasal vasoconstrictors and decongestants and steroids by oral, injection or ophthalmic routes.[1] Although some doctors and their patients have found depot injection of corticosteroids to be helpful, modern developments in treatment should make the use of potent drugs such as triamcinolone less appropriate.

Antihistamines

The traditional antihistamines have served a useful function in the treatment of the nasal and eye symptoms of hay fever and also the somewhat more vague general or systemic upset reported by many patients. The major drawback of their use is the side effect of sedation; however this differs markedly among hay fever sufferers, and for many patients chlorpheniramine is an effective and acceptable form of treatment.[2] Chlorpheniramine or one of the other alkylamine antihistamines tend to be used as a standard against which other drugs are compared. There is little to suggest, however, that any of the other 'older generation' antihistamines offer any appreciable benefit over chlorpheniramine. In a general practice study ketotifen, in doses of 1 mg or 2 mg, twice daily, was compared with chlorpheniramine 12 mg twice daily (sustained release formulation) and placebo in hay fever and allergic rhinitis.[3] The results suggest a superiority for ketotifen over chlorpheniramine or placebo only on some parameters and an apparent advantage of ketotifen 1 mg twice daily rather than 2 mg twice daily.[3]

The introduction of non-sedating histamine H_1-receptor antagonists (the 'newer generation' antihistamines) has resulted in an improvement in the treatment of allergic rhinitis and conjunctivitis.[4] Terfenadine was the first of these new drugs to be introduced, followed by astemizole. The pharmacokinetics of these two drugs are different, terfenadine having a rapid onset and offset of action, and astemizole having a slower onset of action and longer half-life. The main effects of these drugs are said to be on sneezing, rhinorrhoea and conjunctivitis, rather than on nasal blockage.[5] A topical steroid should be considered if this latter symptom presents a problem. Several studies have compared terfenadine and astemizole in the treatment of hay fever. In one study astemizole was found to be more effective than placebo or terfenadine at controlling itchy eyes, sneezing and runny nose but not blocked nose,[6] while in a general practice study both drugs seemed to be well accepted by patients and relatively free of side effects.[7] The patients' own assessments of symptom severity suggest that control during June and July was better with astemizole.[7] Terfenadine was found to be as effective as chlorpheniramine at improving all symptoms of allergic rhinitis and conjunctivitis in a multicentre study.[8]

With regard to onset of action, patients taking terfenadine have noticed alleviation of their symptoms within hours whereas those taking astemizole noticed it within days.[9] It was originally suggested by the manufacturers that a loading dose of 20–30 mg of astemizole daily for up to seven days might be used to hasten onset of action by reaching 'steady-state' blood levels more quickly. Astemizole's place in management has evolved towards maintenance therapy and in an attempt to simplify the dosage regimen the use of a loading dose is no longer recommended.

In a study comparing the effect of terfenadine and placebo on symptoms after nasal allergen provocation with birch pollen in sensitive patients, terfenadine treated patients had a statistically significant reduction in sneezing and nasal secretion 10 minutes after provocation, compared with those treated with placebo (although there was no significant difference in nasal secretion over the entire 90-minute study period).[10] When nasal blockage was studied using the technique of rhinomanometry no significant difference between terfenadine and placebo could be identified, supporting the view that although sneezing and rhinorrhoea are mediated significantly by histamine, nasal blockage is not. It has been suggested that terfenadine is subject to some loss of effectiveness when taken over an extended period of time but this tachyphylaxis was not demonstrated when terfenadine was studied in the treatment of chronic dermographic urticaria.[11]

More recent additions to the new group of antihistamines are loratadine and cetirizine. In a double-blind study of loratadine (10 mg, once daily), mequitazine (5 mg, twice daily) and placebo in the symptomatic treatment of seasonal allergic rhinitis both active treatments were found to be significantly more effective

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than placebo in reducing total symptoms and nasal symptoms.[12] Other new developments include the selective H_1-receptor antagonist levocabastine. Its effect has been studied in a nasal and conjunctival provocation test,[13] and a significant improvement in the symptoms of rhinorrhoea and sneezing were demonstrated but not in nasal blockage; a significant protective effect against eye symptoms was also shown.[13] There is pharmacological evidence in rats that levocabastine is 15 000 times more potent than chlorpheniramine.[13]

Nasal steroids

Corticosteroids applied topically to the muscosa clearly have a part to play in the treatment of seasonal allergic rhinitis. There is no reported evidence of any significant systemic absorption or of any other troublesome adverse effect. Corticosteroids are likely to be most effective against nasal blockage but obviously lack any more general effects and separate eye medication may also be required. Not only does it seem safer to avoid systemic corticosteroids but topical steroids have been shown to have advantages in the treatment of hay fever.[14] Pre-seasonal treatment with topical steroids is recommended to reduce symptoms and mediator release during both early and late reactions in the nose. In contrast, systemic corticosteroids have been reported to have no effect on the early response. The three main drugs in this group are beclomethasone, flunisolide and budesonide.

Beclomethasone dipropionate has been shown to be effective in both alleviating and preventing the nasal symptoms of allergic rhinitis when applied topically. It is available in two forms, as a pressurized aerosol and an aqueous nasal spray and comparison of the two presentations demonstrated equivalent efficacy.[15] In one study however more patients were reported to prefer the aqueous spray to the aerosol.[16] Flunisolide is also available in a similar choice of presentations. Budesonide is a nonhalogenated glucocorticosteroid with high lipid solubility and negligible water solubility. Hay fever patients sensitive to birch pollen have been studied before and during the pollen season comparing those pre-treated with budesonide (200 mg twice daily) with controls.[17] No difference was demonstrated between the two groups in the seasonal increase in epithelial mast cells but a statistically significant reduction in tissue histamine content was observed in patients receiving steroid treatment. It was suggested that this might be due to an inhibition of the intracellular synthesis of histamine or an increased degradation rate of the available histamine.

Budesonide and beclomethasone aerosols have been compared in the treatment of ragweed-induced rhinitis using a double-dummy technique.[18] Both medications were taken only when needed. During the seven-week study budesonide demonstrated greater clinical potency than beclomethasone in that fewer applications were needed to control the rhinitis. In some patients in both groups additional treatment with oral chlorpheniramine was needed to maintain good symptom control. There were few side effects; stinging of the nasal mucosa on application was reported significantly more often after beclomethasone than after budesonide.

The ability of beclomethasone nasal solution, flunisolide and sodium cromoglycate to relieve symptoms of ragweed allergy have been compared.[19] Both nasal steroids were found to be superior to sodium cromoglycate although neither flunisolide nor beclomethasone nasal solution totally controlled patients' symptoms and sodium cromoglycate was superior to placebo. Flunisolide nasal spray effectively relieved eye symptoms compared with beclomethasone, sodium cromoglycate or placebo but flunisolide treated patients reported more side effects such as transient mild stinging or burning on application. It has been suggested that the side effects of nasal steroids can be minimized by the use of a saline nasal spray at intervals between the applications of the steroid.[20] There was an apparent preventive effect on seasonal asthma for patients treated with any of the three active drugs.

Cromoglycate and nedocromil sodium

Sodium cromoglycate administered topically to the nose in hay fever does not seem as successful as when inhaled in asthma. It has to be administered at regular intervals during the day and may take several days to produce maximal benefit.[21] The combination of sodium cromoglycate with a 0.025% concentration of the vasoconstrictor xylometazoline hydrochloride has been found to be more effective than placebo in treating seasonal allergic rhinitis.[21] It has been suggested that this combination should, with sensible use, present no problems with the rebound hyperaemia of rhinitis medicamentosa.[21] Sodium cromoglycate applied to the eyes, either as drops or ointment, is an effective remedy for allergic conjunctivitis and may be used as an adjunct to nasal or other treatment or as the sole therapy.

Nedocromil sodium is a new pyranoquinoline dicarboxylic acid derivative reported to be active against both mucosal and connective tissue-type mast cells. It is now available in the UK for the treatment of asthma. In a comparison of intranasal nedocromil sodium with placebo in the treatment of ragweed allergic rhinitis[22] a statistically significant benefit was recorded for nedocromil sodium over placebo for nasal discharge and eye itch with all symptoms reported to be less with nedocromil sodium than with placebo. There was also significantly less 'rescue' antihistamine used by patients on nedocromil sodium compared with placebo. The apparent benefit of nasally applied nedocromil for eye symptoms is interesting. In a double-blind comparison of nedocromil sodium (1% nasal spray) and placebo in rhinitis caused by birch pollen both the patients and the investigators favoured nedocromil but the only statistically significant difference was that less 'rescue' antihistamine tablets were used by patients on nedocromil sodium compared with those on placebo.[23]

Immunotherapy

Attempts to reduce patients' sensitivity to allergens have been made for more than 70 years.[24] The technique originally described as desensitization has since reduced its claim to hyposensitization but the term currently in vogue is immunotherapy. Until recently subcutaneous immunotherapy has been used but oral or nasal routes have now been explored and these are discussed later.

Since October 1986 immunotherapy in the UK has been effectively limited to hospital practice. The Committee on Safety of Medicines recommended that 'such treatment should only be carried out where facilities for full cardiorespiratory resuscitation are available, and patients should be kept under medical observation for at least two hours after treatment'.[25] This gave official backing to the opinion of many clinicians that evidence in support of the efficacy of vaccines other than ragweed extracts, bee and wasp venoms, and the vaccines used to protect against anaphylaxis induced by some antibiotics, was not sufficient to balance the potential of these agents to induce allergic type reactions, the most serious being bronchospasm and anaphylaxis.[25] In the UK 26 deaths from anaphylaxis caused by desensitizing vaccines were recorded between 1957 and 1986. Eleven of these deaths occurred between 1980 and 1986 and five in the 18 months prior to the Committee's report in October 1986. Under-reporting of such events may mean that these figures underestimate the real risk of anaphylaxis. Although absolute numbers of serious reactions may be small, doctors involved

in such cases have no difficulty in deciding on their subsequent choice of therapy for allergic disorders and firmly held opposition to immunotherapy has existed for many years.[26]

Interest in allergen polymers, allergoids, oral immunotherapy and nasal immunotherapy has been stimulated by the need for safer forms of immunotherapy.

Action of immunotherapy

Originally, a satisfactory scientific explanation for the action of immunotherapy was lacking but studies now suggest that a number of immunochemical changes are activated. Immunotherapy is thought to lead to the generation of specific immunoglobulin(Ig)G-blocking antibodies to the antigen, to a reduction of IgE antibody levels blunting the usual seasonal increase in IgE levels, to a reduction in mast cell and basophil degranulation in response to allergen challenge and to stimulation of T-lymphocyte suppression of IgE production.[20] Levels of IgE and IgG have been studied in children with birch pollinosis given immunotherapy for three years using either birch alone or a mixture of birch, elder and hazel pollen preparations.[27] Clear correlations between the antibody levels and clinical improvements were not found but the development of new sensitivities were noted in a proportion of the children, apparently without clinical implications. In another study using birch pollen extract the abolition of eosinophil chemotactic activity was demonstrated in the serum of allergic patients during the birch pollen season.[28]

Allergen polymers, allergoids and mixed pollen preparations

The safety and immunogenicity of immunotherapy with individually polymerized tree allergens in patients with multiple inhalant sensitivities has been demonstrated and also the safety of administering individually polymerized tree allergens, individually polymerized grass allergens and polymerized ragweed allergen simultaneously in such patients.[29] No systemic reactions were reported in the 16 patients studied. A double-blind placebo-controlled trial of polymerized whole grass administered in an accelerated dosage schedule for immunotherapy of grass pollinosis has demonstrated the safety and effectiveness of individually polymerized grass and also an associated rise in levels of grass-pollen-specific IgG blocking antibody.[30]

In an attempt to reduce the length of time involved in completing the procedure, 'rush' immunotherapy regimens have been developed. Rush immunotherapy with allergoids and standardized orchard grass-pollen extracts has been studied in a double-blind placebo-controlled study in the northern Mediterranean area.[31] Allergoids are grass pollen or other allergen mixtures modified by physicochemical methods to reduce their allergenicity while retaining their immunogenicity in an attempt to minimize systemic reactions. Rush immunotherapy with both the standardized grass-pollen extracts and the allergoids had a significant benefit over placebo in terms of symptomatic improvement and also reduction of skin test sensitivity and increase in levels of grass-pollen-specific IgG although not significantly in respect of change in levels of grass-pollen-specific IgE.[31] There was no significant difference between the two treatment groups, although the trend was in favour of the standardized grass-pollen extracts. Systemic reactions did, however, occur with both treatment groups and this study does not support the concept that allergoids will retain immunogenicity and lose allergenicity. Immunotherapy with a high molecular weight formalinized allergoid has been studied in a double-blind placebo-controlled trial of grass-pollen allergy.[32] Of the 39 patients who received active immunotherapy six patients presented systemic reactions and one patient with a more severe reaction required treatment with adrenaline. Patients in the active group tolerated nasal provocation testing significantly better than the control group and had a significant reduction in symptoms during the peak of the season. Serum grass-pollen IgE levels were significantly increased after immunotherapy.

Immunotherapy with a birch pollen preparation alone has been compared with one made from a mixture of birch, elder and hazel.[33] The mixed extract was found to be at least as effective as the birch alone even in a region where birch is the dominant pollen from deciduous trees. After two years of treatment the mixed preparation gave a better result than equipotent birch allergen preparation although the difference was small.

Two regimens using a polyethylene glycol modified ragweed extract have been compared.[34] A weekly regimen of preseasonal injections of modified ragweed was found to be preferable to a modified rush regimen where the dose was increased daily until there was an adverse reaction. It was commented that 'adverse reactions can occur despite careful attention to the effects of serial injections and appropriate modification of the dosage administered'.

Oral immunotherapy

Oral immunotherapy in birch pollen hay fever has been studied in Scandinavia.[35] In a double-blind placebo-controlled trial using enterosoluble capsules reaching a cumulated dose about 200 times higher than the dose used in conventional subcutaneous immunotherapy there was a significant decrease in eye symptom scores and conjunctival sensitivity and a decrease (albeit not statistically significant) in nasal symptom scores, nasal sensitivity and need for rescue antiallergic medication. Some gastrointestinal side effects were reported but no anaphylactic reactions and only one case of urticaria. In South Africa the efficacy of grass-maize pollen oral immunotherapy in patients with seasonal hay fever has been studied.[36] During the first year of the study patients on active therapy had significantly fewer hay fever symptoms in the summer months than those on placebo and the extract appeared to be well tolerated.

Nasal immunotherapy

Local nasal immunotherapy has been considered in an attempt to overcome systemic effects, having been successful with moderate doses of aqueous allergen extract.[37] However, it is associated with appreciable local adverse reactions and reduction of the allergen dose to minimize these means that symptoms are no longer prevented.[38] The clinical effectiveness of local nasal immunotherapy with high-dose polymerized ragweed extract in reducing allergic nasal symptoms but not allergic eye symptoms has been demonstrated.[39] The treatment was well tolerated with no serious adverse reactions. This form of immunotherapy stimulated nasal secretory ragweed-specific IgA and IgG but the seasonal rise in serum ragweed-specific IgE was not blocked.

Children

For the many children who suffer from hay fever, oral antihistamines, often in liquid form, provide satisfactory management in many cases, although an idiosyncratic response to antihistamines can occur in children.

A multi-centre double-blind placebo-controlled trial of terfenadine suspension in the treatment of 'fall' allergic rhinitis in children aged six to 12 years suggested that treatment with terfenadine provided effective symptom relief in 85% of patients, although placebo was effective in 60% of cases.[40] No adverse effects were reported. Another study compared terfenadine suspension with placebo in the treatment of children aged six

to 12 years suffering from grass-pollen induced allergic rhinoconjunctivitis and skin and conjunctival reactivity outwith the pollen season;[41] significant inhibition of the type 1 allergic reaction was found with terfenadine without any significant adverse effects.

Other forms of treatment

Oligo-allergenic diets have been advocated where food intolerance may be playing a part in the symptoms of rhinitis.[42] It is unlikely, however, that rhinitis is causally related to food ingestion.[20]

In a carefully controlled trial of a homoeopathic preparation among hay fever sufferers[43] it was shown that patients taking the homoeopathic preparation had a greater improvement in symptoms than those taking placebo. The homoeopathic preparation used (mixed grass pollens) was 'potentized' to the point where, in theory, none of the original material remained but despite this, the preparation caused occasional aggravations of symptoms, thus casting doubt on the absolute safety of these preparations.

Theophylline at therapeutic concentrations has been demonstrated to inhibit the appearance of histamine in nasal secretions during antigen-induced rhinitis.[44]

Choice of treatment

Most studies of the treatment of rhinitis utilize patients' subjective symptom ratings as a measure of the severity of the disease. The 10 cm visual analogue scale is frequently used, although its validity has been questioned by some researchers.[45] In this study, patients' own overall symptom severity rating on a visual analogue scale was compared with symptom scores on a four-point scale: statistical correlation was found in untreated patients during the pollen season, including a summed symptom score (results in pollen or histamine challenged patients were less conclusive).[45] However, the use of summed symptom scores was not advised.

In a series of comparative trials, nine regimens for the treatment of hay fever were tried in 640 patients.[46] Patients' assessments of the usefulness of the treatments (degree of symptoms, side effects, ease of use) were recorded. The highest overall usefulness score was for beclomethasone dipropionate nasal spray with sodium cromoglycate eye drops. However, this was not a significantly higher score than that of methylprednisolone acetate depot injection, oral astemizole or oral terfenadine. It was significantly higher than scores for oral mequitazine, oral chlorpheniramine, sodium cromoglycate nasal insufflation with xylometazoline/antazoline eye drops and oral azatadine maleate. Dimethothiazine was also shown to be useful but has subsequently been withdrawn. A survey of the treatment of hay fever in a small English town found that only 19% of the secondary school children with allergic rhinitis were using nasal sprays.[47] The most favoured treatment was tablets, most commonly chlorpheniramine. Twice daily nasal beclomethasone dipropionate has been compared with once daily oral astemizole in a double-blind double-dummy comparative study and the results suggested that oral astemizole was at least as good as nasal beclomethasone in the maintenance treatment of hay fever and that it offered the additional advantage of improved control of eye symptoms.[48]

Choice of treatment depends, as always, on the individual circumstances of the patient and his or her disease. It should be remembered that the suffering caused by hay fever can range from annoyance to major discomfort. However, hay fever is not life threatening and the optimum treatment must be correspondingly safe and effective while producing as few adverse effects as possible.

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